Insulinoma. Diagnostic criteria and treatment

Introduction
The insulinoma is the most frequent functioning pancreatic endocrine tumor. It is characterized by the autonomous production of insulin by the beta cells of the pancreatic islets. Its incidence is of 4 cases per million of population and year, with a peak between the third and sixth decades of life, though it might be diagnosed at any age. Most of the series describe a slight predominance in women.

The 90% of the insulinomas are unique tumors, with a size lower than 2 cm and of benign nature. They are located in the same way in the head, the body and the pancreatic tail. They are sporadic, but in 6% of the cases they are part of the multiple endocrine neoplasia type 1 (MEN 1), especially in young patients, with multiple tumors or that associate other endocrinous pathologies. The malignant insulinoma is less frequent (5-12% of the cases) and there are not anatomopathological criteria for its diagnosis. The diagnosis of the malignity is based on the demonstration of the existence of metastasis, in most of the cases of ganglionic or hepatic nature, which are present at the moment of the diagnosis.

Abstract
Insulinomas are rare islet cell tumors of the pancreas. Ninety percent are sporadic, usually single and small. The autonomous insulin secretion results in hypoglycaemia, mostly fasting hypoglycaemia, with neuroglucopenic symptoms. Biochemical diagnosis is established by demonstrating an endogenous hyperinsulinism pattern during a spontaneous or fasting-induced episode of hypoglycaemia. High resolution computer tomography and endoscopic ultrasonography are the preferred imaging techniques for diagnosis before surgery, localizing almost 100% of tumors. Other procedures are used only in selected cases. Surgery removal of insulinoma is the treatment of choice resulting in high overall cure rates. In cases of refractory hypoglycaemia medical management using drugs as diazoxide may be used. Currently, novel therapeutic approaches are being developed.

Keywords: hypoglycaemia, hiperinsulinism, insulinoma, pancreatic neuroendocrine tumors.

Resumen
Los insulinomas son tumores poco frecuentes derivados de las células beta de los islotes pancreáticos. En el 90% de los casos son esporádicos, únicos y de pequeño tamaño. La secreción autónoma de insulina da lugar a hipoglucemias, preferentemente de ayuno, con síntomas neuroglucopépticos. El diagnóstico bioquímico se basa en la demostración de un patrón de hiperinsulinismo endógeno durante un episodio de hipoglucemia espontánea o inducida por el ayuno. La tomografía computarizada de alta resolución y la ecografía endoscópica constituyen los métodos de elección para el diagnóstico prequirúrgico, ya que localizan prácticamente el 100% de los tumores; otras técnicas se reservan para casos seleccionados. La cirugía es el tratamiento de elección, con la que se obtienen altas tasas de curación. Para el control de la hipoglucemia refractaria se utilizan determinados fármacos, como el diazóxido. Actualmente, se encuentran en fase de desarrollo nuevas estrategias terapéuticas.

Palabras clave: hipoglucemia, hiperinsulinismo, insulinoma, tumores neuroendocrinos del páncreas.
Clinical report

The hypoglycemia diagnosis is based on the documentation of the triad of Whipple: low level of plasmatic glucose with symptoms and/or signs of hypoglycemia that are solved after the normalization of the glycemia. The insulinoma is, after the factitious hypoglycemia, the most frequent cause of hypoglycemia in the apparent healthy patient. It produces a fasting hypoglycemia of a characteristic way, usually at dawn, during fasting period and after physical exercise. It is important to remember that the patients with insulinoma might show also a postprandial hypoglycemia. The 75% of the patients show hypoglycemia only during fasting periods, 21% associates postprandial hypoglycemias and 6% only postprandial hypoglycemia.

The clinical expression of insulinoma is often unspecific and variable, even in a same patient, entailing, a mean delay in the diagnosis of 2 years together with the difficulty of documenting hypoglycemia. The adrenergic manifestations of hypoglycemia (perspiration, trembling, palpitations, hunger, diaphoresis...) might be absent. The picture is characterized by neuroglycopenic manifestations (changes in the mood state, behavior alterations, weakness, and visual symptoms, reduction of the conscious level and seizure disorders) and it is usual that the patient does not remember the event. It is frequent that the patients with insulinoma are wrongly diagnosed of neurological or psychiatric processes. The hypoglycemia shall be part of the differential diagnosis of the refractory epilepsy.

Biochemical diagnosis

The diagnosis of insulinoma is based on the demonstration of endogenous hyperinsulinism (EH) during a spontaneous hypoglycemia or induced by the fasting. The criteria for the diagnosis of EH have been modified during the last years. Classically, the criteria defined by Marks and Teale in 1996 and then by Service in 1999, are based on the existence of inappropriately high levels of insulin and C-peptide coinciding with hypoglycemia. Afterwards, other measurement parameters have been added, as the pro-insulin levels, considering the higher proportion of this substance secreted in patients with insulinoma, the beta-hydroxibutyrate, as marker of ketosis response during fasting period, and the response of the glycemia after the stimulation with glucagon. This last one allows determining the hepatic reserves of glucagon after the fasting period depleted in healthy individuals. The determination of the oral hypoglycemia is added to this (sulphonylureas in urine) and the anti-insulin antibodies. These parameters have demonstrated a great diagnostic validity in order to determine the differential diagnosis of EH.

Since it is difficult to document a hypoglycemic event spontaneously or after night fasting, the hypoglycemia has to be induced by means of a controlled fasting in most of the patients. The fasting test of 72 hours is still the reference pattern for the insulinoma diagnosis. It is an expensive procedure that requires several days of hospitalization, but it is usually well tolerated by the patients. Though most of the patients experiment hypoglycemia before 72 hours (33% in 12 hours, 65% in 24 hours, 84% in 36 hours and 93% in 48 hours), a reduced number (7%) present insulinoma and negative fasting test after 48 hours. Moreover, a complete suppression of the beta cell in healthy individuals is achieved only after 72 hours of fasting. Therefore, with the aim of achieving the maximum diagnosis precision, the performance of the test of 72 hours is recommended. The negativity of the fasting test in a patient with insulinoma is exceptional. The protocol of the fasting test performance is detailed in table 1.

The fasting test is positive when a hypoglycemia is recorded with a EH biochemical pattern (insulin ≥3 μU/mL, C-peptide ≥0.2 nmol/L, pro-insulin ≥5 pmol/L, beta-hydroxibutyrate ≤2.7 mmol/L, glucose response after i.v. infusion of glucagon >25 mg/dL). The pro-insulin and the C-peptide are the most precise markers, with a sensitivity and a specificity close to 100%. The insulin levels and the ratio glucose/pro-insulin, pro-insulin/insulin and glucose/insulin have a lower diagnostic value, therefore its systematic use is not recommended at present. The development of hypoglycemia is not a sufficient criterion to give as positive the fasting test, due to the superposition with healthy individuals, especially in young women and children.

Differential diagnosis

The differential diagnosis of the insulinoma is performed with the other causes of hyperinsulinemic hypoglycemia (HH) in apparently healthy individuals. The factitious hypoglycemia produced an undistinguishable biochemical pattern by the abrupt determination of sulphonylurea-
as, but the drug can be measured in urine. The C-peptide will be suppressed in the cases of exogenous administration of insulin (table 2).

The nesidioblastosis or islet cell hyperplasia is not so frequent due to HH in adults. It might be congenital (related to mutations in the insulin receptor) or induced by the abrupt determination of sulphonylureas or the surgery of gastric derivation. Unlike the insulinoma, the hypoglycemia is of postprandial presentation, and the fasting test is negative. The usual imaging techniques are negative; therefore one has to resort to more sensitive methods in order to determine the diagnosis. The non insulinoma pancreatic hypoglycemia (diffuse hypertrophy of the islets cells) and hypoglycemia of autoimmune origin are exceptional.\textsuperscript{12}

### Localization

At present we count with a multitude of techniques to determine the localization of the insulinoma. By means of the use of intraoperatory ultrasounds and the pancreatic palpation by an experienced surgeon, 100\% of the insulinomas are detected.\textsuperscript{13} The intraoperatory echography has a sensitivity higher than 95\% and it also provides anatomic information when localizing the duct system and the intra-pancreatic vessels, allowing to plan the type of surgery and reduce the number of complications. The 75\% of the tumors are identified by means of pancreatic palpation (it shows limitations in the small tumors), of soft consistency and deep situation in the pancreas.\textsuperscript{14}

Since the high precision of the intraoperatory methods, the discussion is focused on the role of the pre-surgery diagnosis. Most of the authors support the pre-surgery localization as it allows planning the type of intervention, choosing a laparoscopic approach, shortening the surgi-

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### Table 1. Fasting test of 72 hours\textsuperscript{10}

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>Insulin (μU/mL)</th>
<th>Pro-insulin (pmo/L)</th>
<th>C-peptide (nmol/L)</th>
<th>Beta-hydroxibutyrate (mmol/L)</th>
<th>Glycemia increase after glucagon (mg/dL)</th>
<th>Anti-insulin anti-bodies</th>
<th>Sulphonylureas in urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55</td>
<td>≥3</td>
<td>≥5</td>
<td>≥0,2</td>
<td>≤2,7</td>
<td>≥25</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Nesidioblastosis</td>
<td>&lt;55</td>
<td>≥3</td>
<td>≥5</td>
<td>≥0,2</td>
<td>≤2,7</td>
<td>≥25</td>
<td>Negative</td>
</tr>
<tr>
<td>Facticious hypoglycemia by insulin</td>
<td>&lt;55</td>
<td>≥3</td>
<td>&lt;5</td>
<td>&lt;0,2</td>
<td>≤2,7</td>
<td>≥25</td>
<td>Negative</td>
</tr>
<tr>
<td>Facticious hypoglycemia by sulphonylureas</td>
<td>&lt;55</td>
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<td>≥5</td>
<td>≥0,2</td>
<td>≤2,7</td>
<td>≥25</td>
<td>Negative</td>
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<tr>
<td>Non-insulinoma hypoglycemia syndrome</td>
<td>&lt;55</td>
<td>≥3</td>
<td>≥5</td>
<td>≥0,2</td>
<td>≤2,7</td>
<td>≥25</td>
<td>Negative</td>
</tr>
<tr>
<td>Autoimmune hypoglycemia</td>
<td>&lt;55</td>
<td>≥3</td>
<td>Variable</td>
<td>Variable</td>
<td>≤2,7</td>
<td>≥25</td>
<td>Positive</td>
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</tbody>
</table>

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### Table 2. Biochemical pattern of insulinoma and differential diagnosis of the hyperinsulinemic hypoglycemia\textsuperscript{10}

<table>
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<th>Glucose (mg/dL)</th>
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<th>C-peptide (nmol/L)</th>
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<td>≥3</td>
<td>≥5</td>
<td>≥0,2</td>
<td>≤2,7</td>
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cal time and reducing the morbimortality. Moreover, the pre-surgical extension study by means of computed tomography (CT) or magnetic resonance (MR) allows performing the screening of the metastasis and its performance is indicated in all the cases with insulinoma. The pre-surgical diagnosis of 100% of the patients can be achieved with the current methods (75% though non-invasive methods). The diagnostic precision of the conventional imaging techniques (abdominal echography, CT) is limited, with a sensitivity of 50-60%. These techniques detect preferably tumors >2 cm of easy intra-operative diagnosis. The new multi-cut helicoidal CT allow to diagnose 94% of the cases, and are included within the option diagnosis methods (figure 1). The modern equipments of MR with the use of gadolinium, contrary to the other techniques, offer a better performance in the small and multiple tumors (<1 cm).

Among the invasive techniques, the endoscopic echography is the choice technique, recommended by most of the authors. It diagnoses 83-100% of the tumors located in the head or the pancreas body, though it is less sensitive for the lesions in the tail (60%). It allows the collection of biopsies and provides excellent anatomic information. The intraductal echography improves the diagnosis precision, but due to its complexity it is reserved for selected cases. The gammagrapy with octreotide has a limited value in the insulinoma study as less than 50% of the cases express receptors of the somatostatine. The positron emission tomography (PET) with fluor-18-L-dihydroxyphenylalanine (18F-DOPA) is a technique which is used in the diagnosis of neuro-endocrino tumors. This technique localizes a great sensitivity of pancreatic tissue that produces the insulin in patients with insulinoma or hyperplasia of beta cells, due to the capacity of the endocrine pancreas to capture and descarboxilate L-DOPA. It has demonstrated a higher validity as regards to the CT or MR in small series and has a promising future in the functional study of the pancreatic tissue, but the study of greater series is necessary to validate its diagnostic precision. The arteriography is an invasive technique and not free from complications, with a variable sensitivity, in the region of 60%, dependent on the tumor size and the level of vascularization, and its use is being abandoned as one disposes of other diagnosis methods.

The selective intra-arterial stimulation with calcium, by means of the measurement of insulinemia in the suprahepatic veins and the record of insulin secretion in specific territories is getting an increasing protagonism in the regional diagnosis of the insulinoma. Its sensitivity is of 90%, clearly higher than the echography, the CT and the MR. The access is through the femoral route and the venous catheter is placed (Swan Ganz catheter) in the suprahepatic vein for the collection of insulinemia samples. Through the arterial catheter the stimulation takes place selectively with calcium gluconate in the arteries that irrigate the pancreatic head (gastroduodenal and superior mesenteric) the body and the tail (splenic artery) and samples are collected in venous blood of basal insulinemia, after 30, 60 and 120 minutes. The tumoral cells of an insulinoma have an exaggerated response to the calcium stimulation. When stimulating through the gastroduodenal or superior mesenteric artery, the insulinemia rises more than 2-folds over the basal level, the tumor will be localized in the pancreas head or neck. If when stimulating the splenic artery the described effect is produced, the tumor will be localized in the body and the tail of the pancreas.

To summarize, the performance of a pre-surgical study with multi-cut helicoidal CT and endoscopic echography allows the localization of the insulinoma with a sensitivity of 100% and a specificity of 95%. The PET with 18F-DOPA and the rest of the invasive procedures (arteriography and selective intra-artery stimulation with calcium), due to its high cost and its scarce accessibility, are reserved for patients with biochemical EH confirmation when the rest of the studies are negative.

Figure 1. Angio-CT of the insulinoma. Angio-CT of high resolution (hepatopancreatic window) in which an insulinoma of 14 mm is identified in the pancreas head, increased uptake in arterial phase.
and in patients with MEN 1 or with multiple tumors suspicion.

**Treatment**

The surgical extirpation of the insulinoma is the choice treatment and the only healing one, achieving remission rates of 75-98%. The surgery might be either open or laparoscopic. The enucleation and the pancreatic resection by laparoscopy have been performed with success at many sites and they offer all the advantages of a minimally invasive surgery, with a lower hospital stay and a faster recovery. Though the complications are relatively frequent as the pancreatic fistula (from 18 to 33%, according to the series), they do not entail neither increase of morbidity nor hospitalization days.

The intra-operative laparoscopic ultrasonography (US Lap) might facilitate the localization of the lesion and minimize the need of conversion to open surgery. The laparoscopy shall not be done in case of tumors localized in the pancreatic head, given the high risk of hemorrhage that it entails (up to 20-40% of the cases), so this route should be reserved for the patients with solitary lesions in the body and tail of the pancreas who have not undergone another pancreatic intervention previously and an experienced team should do it. The enucleation is indicated in small tumors located at least at 2-3 mm of the principal pancreatic conduct. The recent guidelines suggest that it is sufficient with the enucleation if the lesion is superficial and is clearly defined in the intra-operative process.

The widened resection is recommended when the tumor invades the pancreatic conduct or the big vessels, or when malignity is suspected by invasion of the peripheral tissues, dilatation of the pancreatic conduct or affection of the lymphatic ganglions. The different options of resection include the distal pancreatectomy (with or without splenectomy), the technique of Whipple or the almost total pancreatectomy, according to the localization of the insulinoma. The intra-operative determination of the insulinemia levels might be useful to ensure the complete resection of the tumor.

In patients with MEN 1 syndrome, the insulinomas are usually multiple up to 59% of the cases versus only 5% in the rest of the patients. Therefore, and considering the high index of post-surgical relapses, it is recommended to perform a subtotal distal pancreatectomy together with the enucleation of the tumors that are located in the pancreas head. A new localization diagnosis should be done in patients with persistent hypoglycemia after surgery and an intervention is recommended by means of the laparotomy. With the application of new techniques of pre-operation localization, especially the combinations of helicoidal CT and endoscopic ultrasonography (with sensitivity close to 100%), a few hidden insulinoma are left out. If the tumor cannot be identified, the “blind” pancreatic resection is not recommended and the patient shall be re-evaluated in order to verify the diagnosis.

The 91% of the intervened patients keep remission criteria 6 months after the surgery. From these ones, 11% experience a recurrent hypoglycemia during the follow-up. Relapses can occur up to 18 years after the intervention. The accumulated incidence of recurrences is of 6% after 10 years and 8% after 20 years. In patients with MEN 1, the recurrence index is higher, reaching 21% after 10 years.

The survival of the patients who underwent surgery is similar to the general population. However, it worsens significantly in advanced age patients and in the patients who show a malignant insulinoma, though it seems to have a long natural history in patients with metastatic disease and more than 20 years of follow-up.

**Treatment of the hepatic metastasis**

The liver is the most common place where the insulinoma metastasis are located, for which there are several direct therapeutic modalities. The hepatic resection is indicated in the absence of diffuse lesions in both lobules, previous hepatic failure and extensive extra-hepatic metastasis (pulmonary, peritoneal...), obtaining higher survival indexes, though the healing is only achieved in 15% of the patients. The therapeutic embolization of the hepatic artery causes necrosis of the tumoral tissue without damaging the healthy hepatic tissue. The selective embolization, with or without infusion of chemotherapeutic substances, is used as palliative techniques in patients with symptomatic hepatic metastasis who are not candidates to surgery. The radiofrequency and the cryo-ablation might be performed subcutaneously or by laparoscopic route, entailing a lower morbidity than the resection of the metastasis or the arterial embolization; there
are no data available about the efficacy at long term. The hepatic transplant has been done in a few patients and the follow-up duration is insufficient to show data about the healing possibility. As regards to the chemotherapy, the traditional choice regime has been the streptozotocine and the doxorubicin, though its modest efficiency (achieves between 10 and 40% of tumoral remission) and its toxicity has promoted the development of new therapeutic agents, as the angiogenesis inhibitors.

Medical treatment
The medical treatment of the insulinoma has to be taken into account in patients with hidden insulinoma, in those who are not candidates to surgery or reject them, and in those who have a non-resectable metastatic disease. The therapeutic options to prevent the symptomatic hypoglycemia are as follows:

- The diazoxide (100-800 mg/day) increases the plasmatic concentration of glucose reducing the insulin secretion, and up to 50% of the patients achieve an improvement in the control of their hypoglycemias. The edema, the gastrointestinal disorders and the hypertricosis are described as side effects.
- The octreotide inhibits the secretion of the growth hormone, but it also inhibits the secretion of TSH, insulin and glucagon in high doses. Its efficacy is limited in the insulinoma. However, it is a reasonable alternative in patients with persistent refractory hypoglycemia as regards to the treatment with diazoxide.
- The lanreotide is another analogue of the somatostatin that seems to have a similar effect to the octreotide and offers the advantage of having a long-acting release form.
- The everolimus is an immunosupressor drug with antiangiogenic effect, with promising results in the glycemic control and the tumoral reduction in patients with malignant insulinoma, even in clinical trials.

Figure 2 shows the diagnosis algorithm that has to be followed before the suspicion of insulinoma.

Conclusions
The biochemical diagnosis and localization of the insulinoma is complex. It requires specific analytical and technical determinations, invasive some times. Almost the total diagnosis of the tumors is achieved with the current methods; therefore the hidden insulinomas are exceptional. The surgery offers high healing rates and the rest of the therapeutic options remain relegated to a second background.
Declaration of potential conflict of interests
M. Diéguez, M. Riestra and E. Menéndez state that there are no conflicts of interest as regards to this article.

References